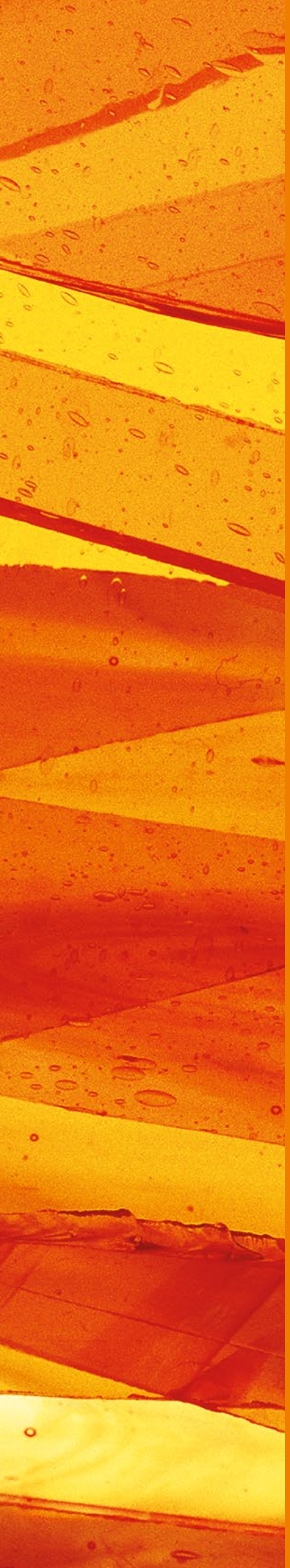

WHO recommendation on **Routes of oxytocin administration for the prevention of postpartum haemorrhage after vaginal birth**

World Health Organization

human reproduction programme hrp
research for impact
UNDP · UNFPA · UNICEF · WHO · WORLD BANK

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Acronyms and abbreviations

CerQUAL	Confidence in the Evidence from Reviews of Qualitative Research
DOI	declaration of interest
ERG	Evidence Review Group
ESG	Evidence Synthesis Group
EtD	Evidence to Decision
FIGO	International Federation of Gynecology and Obstetrics
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSG	Guideline Steering Group
HRP	UNDP–UNFPA–UNICEF–WHO–World Bank Special Programme of Research, Development and Research Training in Human Reproduction
ICM	International Confederation of Midwives
IM	intramuscular
IU	international units
IV	intravenous
MPH-GDG	WHO Maternal and Perinatal Health Guideline Development Group
PICO	population (P), intervention (I), comparator (C), outcome (O)
PPH	postpartum haemorrhage
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization

Executive summary

Introduction

Postpartum haemorrhage (PPH) is commonly defined as a blood loss of 500 mL or more within 24 hours after birth and affects about 5% of all women giving birth around the world. Globally, nearly one quarter of all maternal deaths are associated with PPH and, in most low-income countries, it is the main cause of maternal mortality. Improving care during childbirth to prevent PPH is a necessary step towards the achievement of the health targets of the third Sustainable Development Goal (SDG 3), particularly target 3.1: reduce the global maternal mortality ratio to less than 70 per 100 000 live births by 2030. Efforts to prevent and reduce morbidity and mortality due to PPH can help to address the profound inequities in maternal and perinatal health globally. To achieve this, skilled health personnel, health managers, policy-makers and other stakeholders need up-to-date and evidence-informed recommendations to guide clinical policies and practices.

In 2019, the Executive Guideline Steering Group (GSG) for World Health Organization (WHO) maternal and perinatal health recommendations prioritized the updating of the existing WHO recommendations for intravenous (IV) versus intramuscular (IM) oxytocin for prevention of PPH after vaginal birth in response to the availability of new evidence. The recommendation in this document thus supersedes the previous WHO recommendations for the prevention of PPH as published in the 2012 guideline, *WHO recommendations for the prevention and treatment of postpartum haemorrhage*.

Target audience

The primary audience for these recommendations includes health professionals who are responsible for developing national and local health-care guidelines and protocols (particularly those related to PPH prevention and treatment) and those involved in the provision of care to women and their newborns during labour and childbirth, including midwives, nurses, general medical practitioners and obstetricians, as well as managers of maternal and child health programmes, and relevant staff in ministries of health and training institutions, in all settings.

Guideline development methods

The updating of these recommendations was guided by standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development*. The recommendations were initially developed and updated using this process, namely: (i) identification of priority questions and outcomes; (ii) retrieval of evidence; (iii) assessment and synthesis of evidence; (iv) formulation of the recommendations; and (v) planning for the dissemination, implementation, impact evaluation and future updating of the recommendations.

The scientific evidence supporting the recommendation was synthesized using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. An updated systematic review was used to prepare the evidence profiles for the prioritized question. WHO convened a meeting on 11–12 March 2020 where the Guideline Development Group (GDG) members reviewed, deliberated and achieved consensus on the strength and direction of the recommendation presented herein. Through a structured process, the GDG reviewed the balance between the desirable and undesirable effects and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity.

Recommendation

The GDG reviewed the balance between the desirable and undesirable effects and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity. The GDG issued the new recommendation on IV versus IM oxytocin for prevention of PPH after vaginal birth, with remarks and implementation considerations. To ensure that the recommendation is correctly understood and applied in practice, guideline users may want to refer to the remarks, as well as to the evidence summary, including the considerations on implementation.

WHO recommendation on routes of oxytocin administration for the prevention of postpartum haemorrhage after vaginal birth

The use of oxytocin (10 international units [IU], intramuscular / intravenous) is recommended for the prevention of postpartum haemorrhage for all births. In situations where women giving birth vaginally already have intravenous access, the slow intravenous administration of 10 IU oxytocin is recommended in preference to intramuscular administration.

(Context-specific recommendation)

Justification

- There is clear evidence in favour of intravenous oxytocin in terms of health outcomes. When compared to intramuscular oxytocin, intravenous oxytocin reduces the risk of postpartum haemorrhage, severe postpartum haemorrhage, blood transfusion and severe maternal morbidity, with no clear differences in undesirable effects. While it is uncertain whether intravenous administration is more cost-effective, routine intravenous oxytocin use for postpartum haemorrhage prevention imposes additional resource requirements, may negatively impact women's comfort and can increase health inequities. The feasibility of intravenous administration may also vary in different settings. However, in situations where intravenous access is already in place at vaginal birth, the clinical benefits of intravenous administration outweigh these other considerations.

Remarks

- The Guideline Development Group acknowledged that either intravenous or intramuscular oxytocin is effective in preventing postpartum haemorrhage and both routes of administration are currently recommended by WHO for this indication.
- While noting that the balance of effects favours intravenous oxytocin for important health outcomes, the Guideline Development Group placed its emphasis on other considerations (including feasibility and impacts on resources, health equity and women's comfort), as well as studies suggestive of possible safety concerns with a rapid intravenous bolus of oxytocin. In instances where women already have intravenous access (for another medical indication), it is recommended to administer oxytocin intravenously.
- The Guideline Development Group acknowledged existing WHO recommendations against the routine use of intravenous fluids during labour and childbirth, with emphasis on the widespread and unnecessary use of routine administration of intravenous fluids for all women in labour in many health facilities in low-middle and high-income settings that increases cost and impacts on resource use. The Guideline Development Group emphasized that intravenous access should not be placed routinely for the sole purpose of administering intravenous oxytocin for postpartum haemorrhage prevention.

- The Guideline Development Group noted that the previous trials considered for this question have all administered an oxytocin dose of 10 IU intravenously for postpartum haemorrhage prevention during vaginal birth. However, the speed of injection ranged from 1 minute (for bolus injection) to 40 minutes (for infusion) and volume of dilution from 1 mL (for bolus injection) to 1000 mL of saline (for infusion). There is no direct evidence comparing the different regimens for administering intravenous oxytocin during vaginal birth, and there were no safety concerns (such as hypotension or tachycardia) in trials comparing slow intravenous administration of 10 IU oxytocin over 1 minute with 10 IU intramuscular oxytocin. However, observational studies in women undergoing caesarean section suggest that rapid intravenous injection results in harmful haemodynamic effects. Therefore, the Guideline Development Group suggests avoiding a rapid injection, and agreed that the 10 IU oxytocin dose should preferably be diluted and administered slowly.
- This recommendation reflects available evidence from direct comparison of intravenous versus intramuscular oxytocin during vaginal birth. For women undergoing caesarean section, WHO currently recommends 10 IU for postpartum haemorrhage prevention without preference for intravenous or intramuscular.
- This recommendation does not relate to the use of oxytocin for other obstetric indications (such as labour induction, labour augmentation, or treatment of postpartum haemorrhage).

1. Introduction

1.1 Background

An estimated 295 000 women and adolescent girls died as a result of pregnancy and childbirth-related complications in 2017, and around 99% of these deaths occurred in low-resource settings *(1)*. Obstetric haemorrhage, especially postpartum haemorrhage (PPH), is responsible for more than a quarter of all maternal deaths worldwide *(2)*. In most low-income countries, PPH is the leading cause of maternal deaths. Thus, improving access to safe and effective interventions to prevent PPH is critical to World Health Organization (WHO) strategic priorities (particularly universal health coverage) for achieving the targets of the third Sustainable Development Goal (SDG 3) *(3)*.

International human rights law includes fundamental commitments of States to enable women and adolescent girls to survive pregnancy and childbirth, as part of their enjoyment of sexual and reproductive health and rights, and living a life of dignity *(4)*. WHO envisions a world where "every pregnant woman and newborn receives quality care throughout pregnancy, childbirth and the postnatal period" *(5)*. To provide good-quality care, skilled health personnel at all levels of the health system need to have access to appropriate medications and training in relevant procedures *(6)*. Health-care providers, health managers, health policy-makers and other stakeholders also need up-to-date, evidence-informed recommendations to guide clinical policies and practices to optimize quality of care and improve health-care outcomes.

PPH is commonly defined as a blood loss of 500 mL or more within 24 hours after birth and affects about 5% of all women giving birth around the world *(7,8)*. Severe maternal complications, such as organ dysfunction or death, generally occur following substantial blood loss that compromises maternal haemodynamic stability. Uterine atony is the most common cause of PPH and a leading cause of PPH-related maternal mortality worldwide *(9)*. Genital tract trauma (including vaginal or cervical lacerations and uterine rupture), retained placental tissue or maternal bleeding disorders can cause PPH. Although PPH can occur in any woman, even those without risk factors, grand multiparity, prolonged labour, prior history of PPH and multiple gestation are associated with an increased risk of bleeding after birth *(10)*. In addition, anaemia is a common aggravating factor *(11)*. The majority of PPH-associated complications could be avoided by the use of prophylactic uterotonics during the third stage of labour (that is, the time between the delivery of the baby and complete expulsion of the placenta).

Oxytocin is one such uterotonic and is listed on the *WHO model list of essential medicines* for this indication *(12)*. It is a synthetic cyclic peptide form of the naturally occurring posterior pituitary hormone *(13,14)*. Oxytocin binds to the oxytocin receptor in the uterine myometrium, stimulating contraction of the uterine smooth muscle. Oxytocin can be administered intravenously where its action is almost immediate with a peak in concentration after 30 minutes *(13,14)*. It can also be administered intramuscularly with a slower onset of action taking 3–7 minutes, with a longer-lasting clinical effect of up to one hour *(13,14)*. Oxytocin requires protection from light and must be stored at 2–8 °C *(15)*.

1.2 Rationale and objectives

WHO has established a new process for prioritizing and updating maternal and perinatal health recommendations, whereby an international group of independent experts – the Executive Guideline Steering Group (GSG) – oversees a systematic prioritization of maternal and perinatal health recommendations in most urgent need of updating *(16,17)*. Recommendations are prioritized for updating on the basis of changes or important new uncertainties in the underlying evidence base on benefits, harms, values placed on outcomes, acceptability, feasibility, equity, resource use, cost-effectiveness or factors affecting implementation. The Executive GSG prioritized updating of the WHO recommendations for intravenous (IV) versus intramuscular (IM) oxytocin for prevention

of PPH after vaginal birth in anticipation of the publication of new and potentially important evidence on these interventions.

These updated recommendations were developed in accordance with the standards and procedures in the *WHO handbook for guideline development*, including synthesis of available research evidence, use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[1] and GRADE Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CerQUAL)[2] methodologies, and formulation of recommendations by a Guideline Development Group (GDG) composed of international experts and stakeholders *(18)*. The recommendation published in this document thus supersedes the previous recommendations for IV versus IM oxytocin for prevention of PPH after vaginal birth that were published in 2012 in *WHO recommendations for the prevention and treatment of postpartum haemorrhage (19)*. The primary aim of these recommendations is to improve the quality of care and outcomes for women giving birth, as they relate to PPH and its complications. This recommendation thus provides guidance for use of IV versus IM oxytocin for prevention of PPH after vaginal birth.

1.3 Target audience

The primary audience includes health professionals who are responsible for developing national and local health-care guidelines and protocols (particularly those related to PPH prevention and treatment) and those involved in the provision of care to women during labour and childbirth, including midwives, nurses, general medical practitioners and obstetricians, as well as managers of maternal and child health programmes, and relevant staff in ministries of health and training institutions, in all settings.

This recommendation will also be of interest to women giving birth in a range of resource settings (low to high), as well as members of professional societies involved in the care of pregnant women, staff of nongovernmental organizations concerned with promoting people-centred maternal care, and implementers of programmes.

1.4 Scope of the recommendation

Framed using the Population (P), Intervention (I), Comparison (C), Outcome (O) (PICO) format, the question for this recommendation was:

- For women in the third stage of labour (P), does administration of IV oxytocin for PPH prevention (I) compared with IM oxytocin (C) improve maternal and infant outcomes (O)?

1.5 Persons affected by the recommendation

The population affected by this recommendation includes all pregnant women in low-, middle- or high-income settings.

[1] Further information is available at: http://www.gradeworkinggroup.org/.
[2] Further information is available at: https://www.cerqual.org/.

2. Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development (18)*. In summary, the process included: (i) identification of the priority question and critical outcomes; (ii) retrieval of evidence; (iii) assessment and synthesis of evidence; (iv) formulation of the recommendation; and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendation.

In 2019, IV versus IM oxytocin for prevention of PPH after vaginal birth was identified by the Executive GSG as a high priority for development of a recommendation, in response to new, potentially important evidence on this question. Six main groups were involved in this process, with their specific roles described in the following sections.

2.1 Executive Guideline Steering Group (GSG)

The Executive GSG is an independent panel of 14 external experts and relevant stakeholders from the six WHO regions: African Region, Region of the Americas, Eastern Mediterranean Region, European Region, South-East Asia Region and Western Pacific Region. The Executive GSG advises WHO on the prioritization of new and existing PICO questions in maternal and perinatal health for development or updating of recommendations *(16,17)*.

2.2 WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Department of Sexual and Reproductive Health and Research and the Department of Maternal, Newborn, Child and Adolescent Health and Ageing managed the process of updating the recommendations. The WHO Steering Group drafted the key recommendation questions in PICO format, engaged the systematic review teams and guideline methodologists (that is, the Evidence Synthesis Group [ESG]), as well as the members of the GDG and the External Review Group (ERG) (see below). In addition, the WHO Steering Group supervised the retrieval and syntheses of evidence, organized the GDG meetings, drafted and finalized the guideline document, and will also manage the guideline dissemination, implementation and impact assessment. The members of the WHO Steering Group are listed in Annex 1.

2.3 Guideline Development Group (GDG)

The WHO Steering Group identified a pool of approximately 50 experts and relevant stakeholders from the six WHO regions to constitute the WHO Maternal and Perinatal Health Guideline Development Group (MPH-GDG). This pool consists of a diverse group of experts who are skilled in the critical appraisal of research evidence, implementation of evidence-informed recommendations, guideline development methods, and clinical practice, policy and programmes relating to maternal and perinatal health. Members of the MPH-GDG are identified in a way that ensures geographic representation and gender balance, and there were no perceived or real conflicts of interest. Members' expertise cuts across thematic areas within maternal and perinatal health.

From the MPH-GDG pool, 14 external experts and relevant stakeholders were invited to participate as members of the GDG for updating this recommendation. Those selected were a diverse group with expertise in research, guideline development methods, gender, equity and rights, clinical policy and programmes relating to PPH prevention and treatment.

The 14 GDG members for this recommendation were also selected in a way that ensured geographic representation and gender balance, and there were no important conflicts of interest. The GDG appraised the evidence that was used to inform the recommendation, advised on the interpretation of this evidence, formulated the final recommendation based on the draft prepared by the WHO Steering Group and reviewed and reached unanimous consensus for the recommendation in the final document. The members of the GDG are listed in Annex 1.

2.4 Evidence Synthesis Group (ESG)

WHO convened an ESG composed of guideline methodologists and systematic review teams to conduct or update systematic reviews, appraise the evidence and develop the Evidence to Decision (EtD) frameworks. A systematic review on this question was updated, supported by the Cochrane Pregnancy and Childbirth Group. The WHO Steering Group reviewed and provided input into the updated protocol and worked closely with the Cochrane Pregnancy and Childbirth Group to appraise the evidence using the GRADE methodology. Representatives of the Cochrane Pregnancy and Childbirth Group and a methodologist attended the GDG meeting to provide an overview of the available evidence and GRADE tables and to respond to technical queries from the GDG.

Evidence for the other domains of the GRADE EtD frameworks were obtained from two existing systematic qualitative reviews exploring what matters to women during childbirth and what matters to women and health-care providers in relation to interventions for the prevention of PPH *(20,21)*. A systematic review on the cost-effectiveness of IV versus IM oxytocin (updated to March 2020) was used for evidence in the cost-effectiveness domain in the EtD framework *(22)*. All members of the ESG attended the GDG meetings to provide an overview of the synthesized evidence and to respond to technical queries from the GDG. The members of the ESG are listed in Annex 1.

2.5 External partners and observers

Representatives of the United States Agency for International Development (USAID), the International Confederation of Midwives (ICM) and the International Federation of Gynecology and Obstetrics (FIGO) participated in the GDG meeting as observers. These organizations, with their long history of collaboration with WHO in maternal and perinatal guideline dissemination and implementation, were identified as potential implementers of the recommendations. The list of observers who participated in the GDG meeting is included in Annex 1.

2.6 External Review Group (ERG)

The ERG included six technical experts with interests and expertise in the provision of evidence-based care to prevent and treat PPH. The group was geographically diverse and gender balanced, and the members had no important conflicts of interest. The experts reviewed the final document to identify any factual errors and commented on the clarity of language, contextual issues and implications for implementation. They ensured that the decision-making processes had considered and incorporated contextual values and the preferences of persons affected by the recommendations, health-care professionals and policy-makers. It was not within the remit of this group to change the recommendations that were formulated by the GDG. Members of the ERG are listed in Annex 1.

2.7 Identification of priority questions and outcomes

The priority outcomes were aligned with those from the 2012 *WHO recommendations for prevention and treatment of postpartum haemorrhage (19)*. These outcomes were initially identified through a search of scientific databases for relevant, published systematic reviews and a prioritization of outcomes by the GDG for the 2012 guideline. After due consideration of the recently published core outcome set for prevention and treatment of PPH *(23)*, two additional outcomes – maternal well-being and maternal satisfaction – were included for this update to ensure that evidence synthesis and recommendation decision-making by the GDG were driven by outcomes that are important to women and to ensure that the final set of recommendations would be woman-centred. All the outcomes were included in the scope of this document for evidence searching, retrieval, synthesis, grading and formulation of the recommendation. The list of priority outcomes is provided in Annex 2.

2.8 Evidence identification and retrieval

Evidence to support this update was derived from several sources by the ESG working in collaboration with the WHO Steering Group.

2.8.1 Evidence on the effects of IV versus IM oxytocin for PPH prevention after vaginal birth

An existing systematic review was updated for the purpose of this update *(24)*. This systematic review was the primary source of evidence for this recommendation.

Randomized controlled trials relevant to the key question were screened by the review authors, and data on relevant outcomes and comparisons were entered into the Review Manager 5 (RevMan) software. The RevMan file was retrieved from the Cochrane Pregnancy and Childbirth Group and customized to reflect the key comparisons and outcomes (those that were not relevant to the recommendation were excluded). The RevMan file was then exported to GRADE profiler software (GRADEpro), and GRADE criteria were used to critically appraise the retrieved scientific evidence *(25)*. Finally, evidence profiles (in the form of GRADE summary of findings tables) were prepared for comparisons of interest, including the assessment and judgements for each outcome and the estimated risks.

2.8.2 Evidence on values, resource use and cost-effectiveness, equity, acceptability and feasibility

Evidence from two systematic reviews were used to inform the acceptability, feasibility and equity domains as they relate to the EtD framework for IV versus IM oxytocin administration for the prevention of PPH *(20,21)*. A review of qualitative studies evaluating "what women want" from intrapartum care was used for the acceptability and equity domains relating to medical interventions, feelings about labour and birth, recognition of complications and receiving information on introduced interventions *(20)*. Another qualitative review explored the perceptions on PPH prevention and treatment of health-care providers and women, including the benefits of oxytocin use to prevent PPH and the factors influencing effective use of oxytocin *(21)*. A systematic review of the literature found no direct evidence on the relative cost-effectiveness of IV oxytocin compared with IM oxytocin to prevent PPH *(22)*.

2.9 Certainty assessment and grading of the evidence

The certainty assessment of the body of evidence for each outcome was performed using the GRADE approach *(26)*. Using this approach, the certainty of evidence for each outcome was rated as "high", "moderate", "low" or "very low" based on a set of established criteria. The final rating of certainty of evidence was dependent on the factors briefly described below.

Study design limitations: The risk of bias was first examined at the level of each individual study and then across the studies contributing to the outcome. For randomized trials, certainty was first rated as "high" and then downgraded by one ("moderate") or two ("low") levels, depending on the minimum criteria met by the majority of the studies contributing to the outcome.

Inconsistency of the results: The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed in different studies. The certainty of evidence was not downgraded when the direction of the findings were similar and confidence limits overlapped, whereas it was downgraded when the results were in different directions and confidence limits showed minimal or no overlap.

Indirectness: The certainty of evidence was downgraded when there were serious or very serious concerns regarding the directness of the evidence – that is, whether there were important differences between the research reported and the context for which the recommendation was being prepared. Such differences were related, for instance, to populations, interventions, comparisons or outcomes of interest.

Imprecision: This assessed the degree of uncertainty around the estimate of effect. As this is often a function of sample size and number of events, studies with relatively few participants or events, and thus wide confidence intervals around effect estimates, were downgraded for imprecision.

Publication bias: The certainty rating could also be affected by perceived or statistical evidence of bias to underestimate or overestimate the effect of an intervention as a result of selective publication based on study results. Downgrading evidence by one level was considered where there was strong suspicion of publication bias.

Certainty of evidence assessments are defined according to the GRADE approach:

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The findings of the qualitative reviews were appraised for quality using the GRADE-CERQual tool *(27)*. The GRADE-CERQual tool, which uses a similar conceptual approach to other GRADE tools, provides a transparent method for assessing and assigning the level of confidence that can be placed in evidence from reviews of qualitative research. The systematic review team used the GRADE-CERQual tool to assign a level of confidence (high, moderate, low and very low) to each review finding according to four components: methodological limitations of the individual studies; adequacy of data; coherence; and relevance to the review question of the individual studies contributing to a review finding. Findings from individual cost-effectiveness studies were reported narratively for each comparison of interest.

2.10 Formulation of the recommendation

The WHO Steering Group supervised and finalized the preparation of summary of findings tables and narrative evidence summaries in collaboration with the ESG using the GRADE EtD framework. EtD frameworks include explicit and systematic consideration of evidence on prioritized interventions in terms of specified domains: effects, values, resources, equity, acceptability and feasibility. For the priority questions, judgements were made on the impact of the intervention on each domain to inform and guide the decision-making process. Using the EtD framework template, the WHO Steering Group and ESG created summary documents for each priority question covering evidence on each domain:

- **Effects:** The evidence on the priority outcomes was summarized in this domain to answer the questions: "What are the desirable and undesirable effects of the intervention?" and "What is the certainty of the evidence on effects?" Where benefits clearly outweighed harms for outcomes that are highly valued by women, or vice versa, there was a greater likelihood of a clear judgement in favour of or against the intervention, respectively. Uncertainty about the net benefits or harms, or small net benefits, usually led to a judgement that did not favour the intervention or the comparator. The higher the certainty of the evidence of benefits across outcomes, the higher the likelihood of a judgement in favour of the intervention. In the absence of evidence of benefits, evidence of potential harm led to a recommendation against the intervention. Where the intervention showed evidence of potential harm and was also found to have evidence of important benefits, depending on the level of certainty and the likely impact of the harm, such evidence of potential harm was more likely to result in a context-specific recommendation, with the context explicitly stated within the recommendation.

- **Values:** This domain relates to the relative importance assigned to the outcomes associated with the intervention by those affected, how such importance varies within and across settings, and whether this importance is surrounded by any uncertainty. The question asked was: "Is there important uncertainty or variability in how much women value the main outcomes associated with the intervention?" When the intervention resulted in benefit for outcomes that most women consistently value (regardless of setting), this was more likely to lead to a judgement in favour of the intervention. This domain, together with the "effects" domain (see above), informed the "balance of effects" judgement.
- **Resources:** For this domain, the questions asked were: "What are the resources associated with the intervention?" and "Is the intervention cost-effective?" The resources required to implement IV oxytocin mainly include the costs of providing supplies and training. A judgement in favour of or against the intervention was likely where the resource implications were clearly advantageous or disadvantageous, respectively.
- **Acceptability:** For this domain, the question was: "Is the intervention acceptable to women and health-care providers?" Qualitative evidence from systematic reviews on the views and experiences of women and providers with the prevention and treatment of PPH informed the judgements for this domain *(20,21)*. The lower the acceptability, the lower the likelihood of a judgement in favour of the intervention.
- **Feasibility:** The feasibility of implementing this intervention depends on factors such as the resources, infrastructure and training requirements, and the perceptions of health-care providers responsible for administering it. The question addressed was: "Is it feasible for the relevant stakeholders to implement the intervention?" Qualitative evidence from the systematic reviews on women's and providers' views and experiences with treatment of PPH was used to inform judgements for this domain *(20,21)*. Where major barriers were identified, it was less likely that a judgement would be made in favour of the intervention.
- **Equity:** This domain encompasses evidence or considerations as to whether or not the intervention would reduce health inequities. Therefore, this domain addressed the question: "What is the anticipated impact of the intervention on equity?" The findings of qualitative reviews of evidence and two rapid reviews, as well as the experiences and experiences of the GDG members, were used to inform judgements for this domain *(20,21)*. The intervention was likely to be recommended if its proven (or anticipated) effects reduce (or could reduce) health inequalities among different groups of women and their families.

For each of the above domains, additional evidence of potential harms or unintended consequences are described in the Additional considerations subsections. Such considerations were derived from studies that might not have directly addressed the priority question but provided pertinent information in the absence of direct evidence. These considerations were extracted from single studies, systematic reviews or other relevant sources.

The WHO Steering Group provided the EtD frameworks, including evidence summaries, summary of findings tables and other documents related to each recommendation, to the GDG members two weeks in advance of the GDG meeting. The GDG members were asked to review and provide comments (electronically) on the documents before the GDG meeting. During the GDG meeting (11–12 March 2020), which was conducted under the leadership of the GDG chairperson, the GDG members collectively reviewed the EtD frameworks, and any comments received through preliminary feedback, and formulated the recommendations. The purpose of the meeting was to reach consensus on each recommendation, including its direction and in some instances the specific context, based on explicit consideration of the range of evidence presented in each EtD framework and the judgement of the GDG members. The GDG was asked to select one of the following categories for the recommendation:

- **Recommended:** This category indicates that the intervention should be implemented.
- **Not recommended:** This category indicates that the intervention should not be implemented.
- **Recommended only in specific contexts (context-specific recommendation):** This category indicates that the intervention is applicable only to the condition, setting or population specified in the recommendation and should only be implemented in these contexts.
- **Recommended only in the context of rigorous research (research-context recommendation):** This category indicates that there are important uncertainties about the intervention. With this category of recommendation, implementation can still be undertaken on a large scale, provided it takes the form of research that addresses unanswered questions and uncertainties related both to effectiveness of the intervention or option, and its acceptability and feasibility.

2.11 Management of declarations of interests

WHO has a robust process to protect the integrity of its normative work as well as to protect the integrity of individual experts with whom it collaborates. WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to actual or ostensible conflicts of interest. The disclosure and the appropriate management of relevant financial and non-financial conflicts of interest of GDG members and other external experts and contributors are a critical part of guideline development at WHO. According to WHO regulations, all experts must declare their interests prior to participation in WHO guideline development processes and meetings according to the guidelines for declaration of interest (DOI) for WHO experts *(18)*. All GDG members were therefore required to complete a standard WHO DOI form before engaging in the guideline development process and before participating in the guideline-related processes. The WHO Steering Group reviewed all declarations before finalizing the experts' invitations to participate. Where any conflict of interest was declared, the WHO Steering Group determined whether such conflicts were serious enough to affect an expert's objective judgement in the guideline and recommendation development process. To ensure consistency, the WHO Steering Group applied the criteria for assessing the severity of conflicts of interests as outlined in the *WHO handbook for guideline development* to all participating experts. All findings from the DOI statements received were managed in accordance with the WHO procedures to assure the work of WHO and the contributions of its experts is, actually and ostensibly, objective and independent. The names and biographies of individuals were published online four weeks prior to the meeting. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility, the experts were only required to openly declare such conflicts of interest at the beginning of the GDG meeting and no further actions were taken. Annex 3 shows a summary of the DOI statements and how conflicts of interest declared by invited experts were managed by the WHO Steering Group.

2.12 Decision-making during the GDG meeting

During the meeting, the GDG reviewed and discussed the evidence summary and sought clarification. In addition to evaluating the balance between the desirable and undesirable effects of the intervention and the overall certainty of the evidence, the GDG applied additional criteria based on the GRADE EtD framework to determine the recommendation. These criteria included stakeholders' values, resource implications, acceptability, feasibility and equity. Considerations were based on the experiences and opinions of the GDG members and supported by evidence from a literature search where available. EtD tables were used to describe and synthesize these considerations.

Decisions were made based on consensus, defined as the agreement by three quarters or more of the participants. None of the GDG members expressed opposition to the recommendation.

2.13 Document preparation

Prior to the online meeting, the WHO Steering Group prepared a draft version of the GRADE evidence profiles, the evidence summary and other documents relevant to the GDG's deliberation. The draft documents were made available to the participants of the meeting two weeks before the meeting for their comments. During the meeting, these documents were modified in line with the participants' deliberations and remarks. Following the meeting, members of the WHO Steering Group drafted a full guideline document to accurately reflect the deliberations and decisions of the participants. The draft document was sent electronically to the GDG and the ERG for their final review and approval.

2.14 Peer review

Following review and approval by GDG members, the final document was sent to eight external independent experts (comprising the ERG) who were not involved in the guideline panel for peer review. The WHO Steering Group evaluated the inputs of the peer reviewers for inclusion in this document. After the meeting and external peer review, the modifications made by the WHO Steering Group to the document consisted only of the correction of factual errors and improving language to address any lack of clarity.

3. Recommendation and supporting evidence

The following section outlines the recommendation and the corresponding narrative summary of evidence for the prioritized question. The EtD table, summarizing the balance between the desirable and undesirable effects and the overall certainty of the supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity that were considered in determining the recommendation, is presented in the EtD framework (Annex 4).

The following recommendation was adopted by the GDG. Evidence on the effectiveness of this intervention was derived from the updated systematic review and summarized in GRADE tables (Annex 4). The certainty of the supporting evidence was rated as "moderate" for most of the critical outcomes.

To ensure that the recommendation is correctly understood and appropriately implemented in practice, additional remarks reflecting the summary of the discussion by the GDG are included under the recommendation.

The use of oxytocin (10 international units [IU], intramuscular/intravenous) is recommended for the prevention of postpartum haemorrhage for all births. In situations where women giving birth vaginally already have intravenous access, the slow intravenous administration of 10 IU oxytocin is recommended in preference to intramuscular administration.

(Context-specific recommendation)

Justification

- There is clear evidence in favour of intravenous oxytocin in terms of health outcomes. When compared to intramuscular oxytocin, intravenous oxytocin reduces the risk of postpartum haemorrhage, severe postpartum haemorrhage, blood transfusion and severe maternal morbidity, with no clear differences in undesirable effects. While it is uncertain whether intravenous administration is more cost-effective, routine intravenous oxytocin use for postpartum haemorrhage prevention imposes additional resource requirements, may negatively impact women's comfort and can increase health inequities. The feasibility of intravenous administration may also vary in different settings. However, in situations where intravenous access is already in place at vaginal birth, the clinical benefits of intravenous administration outweigh these other considerations.

Remarks

- The Guideline Development Group acknowledged that either intravenous or intramuscular oxytocin is effective in preventing postpartum haemorrhage and both routes of administration are currently recommended by WHO for this indication *(19)*.
- While noting that the balance of effects favours intravenous oxytocin for important health outcomes, the Guideline Development Group placed its emphasis on other considerations (including feasibility and impacts on resources, health equity and women's comfort), as well as studies suggestive of possible safety concerns with a rapid intravenous bolus of oxytocin. In instances where women already have intravenous access (for another medical indication), it is recommended to administer oxytocin intravenously.

- The Guideline Development Group acknowledged existing WHO recommendations against the routine use of intravenous fluids during labour and childbirth, with emphasis on the widespread and unnecessary use of routine administration of intravenous fluids for all women in labour in many health facilities in low-, middle- and high-income settings that increases cost and impacts on resource use *(28)*. The Guideline Development Group emphasized that intravenous access should not be placed routinely for the sole purpose of administering intravenous oxytocin for postpartum haemorrhage prevention.
- The Guideline Development Group noted that the previous trials considered for this question have all administered an oxytocin dose of 10 IU intravenously for postpartum haemorrhage prevention during vaginal birth. However, the speed of injection ranged from 1 minute (for bolus injection) to 40 minutes (for infusion) and volume of dilution from 1 mL (for bolus injection) to 1000 mL of saline (for infusion). There is no direct evidence comparing the different regimens for administering intravenous oxytocin during vaginal birth, and there were no safety concerns (such as hypotension or tachycardia) in trials comparing slow intravenous administration of 10 IU oxytocin over 1 minute with 10 IU intramuscular oxytocin *(29,30)*. However, observational studies in women undergoing caesarean section suggest that rapid intravenous results in harmful haemodynamic effects *(30,31)*. Therefore, the Guideline Development Group suggests avoiding a rapid injection, and agreed that the 10 IU oxytocin dose should preferably be diluted and administered slowly.
- This recommendation reflects available evidence from direct comparison of intravenous versus intramuscular oxytocin during vaginal birth. For women undergoing caesarean section, WHO currently recommends 10 IU for postpartum haemorrhage prevention without preference for intravenous or intramuscular *(19)*.
- This recommendation does not relate to the use of oxytocin for other obstetric indications (such as labour induction, labour augmentation, or treatment of postpartum haemorrhage).

4. Dissemination, adaptation and implementation of the recommendation

The dissemination and implementation of this recommendation are to be considered by all stakeholders involved in the provision of care for pregnant women at the international, national and local levels. There is a vital need to increase women's access to maternal health care and to strengthen the capacity at health-care facilities of all levels to ensure they can provide high-quality services to all women giving birth. It is therefore crucial that this recommendation be translated into care packages and programmes at country and health-care facility levels, where appropriate.

4.1 Recommendation dissemination

The recommendation will be disseminated through WHO regional and country offices, ministries of health, professional organizations, WHO collaborating centres, other United Nations agencies and nongovernmental organizations, among others. This recommendation will also be available on the WHO website and the WHO Reproductive Health Library.[1] Updated recommendations are also routinely disseminated during meetings or scientific conferences attended by WHO maternal and perinatal health staff.

The recommendation document will be translated into the six United Nations languages and disseminated through the WHO regional offices. Technical assistance will be provided to any WHO regional office willing to translate the full recommendation into any of these languages.

4.2 Adaptation

National and subnational subgroups may be established to adapt and implement this recommendation based on an existing strategy. This process may include the development or revision of existing national guidelines or protocols based on the updated recommendation.

Existing global models such as those for WHO antenatal and intrapartum care guidelines can be adapted to different countries, contexts and individual needs and preferences of women. The conceptual basis of these models is to drive improvements in the quality of maternal health care, by aiming to achieve the best possible physical, emotional and psychological outcomes for the woman and her baby, irrespective of the influence of generic policies that may exist within and across health systems and countries. Both models address relevant health policy, organizational and user-level considerations. These models thus support implementation of WHO recommendations and are intended to be adapted by stakeholders and partners at regional, country and local levels into locally appropriate documents and tools.

The successful introduction of evidence-based policies (relating to updated recommendations) depends on well-planned and participatory consensus-driven processes of adaptation and implementation. These processes may include the development or revision of existing national or local guidelines and protocols, often supported by ministries of health, United Nations agencies, local professional societies and other relevant leadership groups. An enabling environment should be created for the use of this recommendation, including changes in the behaviour of health-care practitioners to enable the use of evidence-based practices.

In the context of humanitarian emergencies, adaptation of the current recommendation should consider the integration and alignment with other response strategies. Additional considerations to the unique needs of women in emergency settings, including their values and preferences, should be made. Context-specific tools and toolkits may be required

[1] Available at: www.who.int/rhl.

in addition to standard tools to support the implementation of the recommendation in humanitarian emergencies by stakeholders.

4.3 Implementation considerations

- Oxytocin should only be given by skilled health personnel who have been trained to safely administer injectable uterotonics.
- Oxytocin is relatively inexpensive and widely available; however, it requires cold chain, refrigerated transport and storage (2–8 °C). In settings where this cannot be guaranteed, the quality, efficacy and effectiveness of oxytocin may be adversely affected.
- It is advised that programmes to implement uterotonics for PPH prevention ensure women are adequately informed in advance about the need to use a uterotonic to prevent PPH, the available uterotonic options, the possible side effects of these options and their rights to choose what care they receive.
- An enabling environment should be created for the implementation of this recommendation, including education to support behaviour change among skilled health personnel to facilitate the use of evidence-based practices.
- National health systems need to ensure that supplies of good-quality uterotonics and the necessary equipment are available wherever maternity services are provided. This includes establishing robust and sustainable regulatory, procurement and effective cold chain, and logistics processes that can ensure good-quality medicines and equipment are obtained, transported and stored correctly.
- Procurement agencies at all levels of supply chains should procure only quality-assured uterotonic medicines, that are labelled for storage at 2–8 °C, in single-use ampoules or vials of oxytocin of 10 IU per mL (10 IU/mL). While some manufacturer labelling may seem to indicate that oxytocin is stable at room temperature, stability may not have been tested in the much warmer conditions that may be prevalent in some countries, and different formulations have different stability characteristics. To prevent its degradation and to safeguard its quality, oxytocin should always be stored in refrigeration, regardless of labelling.

5. Research implications

The GDG identified important knowledge gaps that need to be addressed through primary research, which may have an impact on this recommendation. The following question was identified as one that demands urgent priority:

- What is the optimal effective regimen of IV oxytocin for PPH prevention after vaginal birth?

6. Applicability issues

6.1 Anticipated impact on the organization of care and resources

Implementing this evidence-based recommendation requires resources for sustainable procurement and storage of uterotonic drugs. The GDG noted that updating training curricula and providing training on the recommendation would increase its impact and facilitate its implementation. Standardization of care, by including this recommendation into existing intrapartum and immediate postpartum care packages, can encourage behaviour change in health-care providers.

As part of efforts to implement this recommendation, health system stakeholders may wish to consider the following potential barriers to their application:

- lack of human resources with the necessary expertise and skills to implement, supervise and support recommended practices;
- lack of understanding of changes in recommended interventions among skilled care personnel and systems managers;
- resistance of skilled care personnel to changing from the use of non-evidence-based to evidence-based practices;
- lack of infrastructure to support interventions (such as electricity and refrigeration for temperature-sensitive uterotonics);
- lack of essential equipment, supplies and medicines (such as needles, syringes, gloves and uterotonics);
- lack of effective mechanisms to identify women who are experiencing PPH, in order to trigger PPH management pathways; and
- lack of health information management systems designed to document and monitor recommended practices (such as patient records and registers).

Various strategies for addressing these barriers and facilitating implementation are provided under implementation considerations in section 4.

6.2 Monitoring and evaluating guideline implementation

The implementation and impact of this recommendation will be monitored at the health service, country and regional levels, as part of broader efforts to monitor and improve the quality of maternal and newborn care. The WHO document *Standards for improving quality of maternal and newborn care in health facilities (32)* provides a list of prioritized input, output and outcome measures that can be used to define quality-of-care criteria and indicators and that should be aligned with locally agreed targets. In collaboration with the monitoring and evaluation teams of the WHO Department of Sexual and Reproductive Health and Research and the WHO Department of Maternal, Newborn, Child and Adolescent Health and Ageing, data on country- and regional-level implementation of the recommendation will be collected and evaluated in the short to medium term to assess its impact on national policies of individual WHO Member States. Interrupted time series, clinical audits or criterion-based audits could be used to obtain the relevant data on the use of interventions contained in this guideline.

With regard to PPH prevention, WHO recommends that the coverage of prophylactic uterotonics be used as a process indicator for the monitoring and prevention of PPH *(19)*. The suggested "prophylactic uterotonic coverage indicator" is calculated as the number of women receiving prophylactic uterotonics during the third stage of labour divided by all women giving birth. This indicator provides an overall assessment of adherence to the recommendation included in this guideline.

The use of other locally agreed and more specific indicators (for example, the proportion of pregnant women with IV access already in place given IV oxytocin after vaginal birth) may be necessary to obtain a more complete assessment of the quality of care related to the prevention and treatment of PPH. WHO has developed specific guidance for evaluating the quality of care for severe maternal complications (including PPH) based on the near miss and criterion-based clinical audit concepts *(33)*. Monitoring of the quality of uterotonic drugs available in low-resource settings may help to guide skilled health personnel in selecting the most effective uterotonic option for PPH prevention in the context in which they are working.

7. Updating the recommendation

The Executive GSG convenes annually to review WHO's current portfolio of maternal and perinatal health recommendations and to help WHO prioritize new and existing questions for recommendation development and updating. Accordingly, this recommendation will be reviewed along with other recommendations and prioritized as needed by the Executive GSG. If new evidence that could potentially impact the current evidence base is identified, the recommendation may be updated. If no new reports or information is identified, the recommendation may be revalidated.

Following publication and dissemination of the updated recommendation, any concerns about the validity of the recommendation should be promptly communicated to the guideline implementers, in addition to any plans to update the recommendation.

WHO welcomes suggestions regarding additional questions for inclusion in the updated recommendation. Please email your suggestions to srhmph@who.int.

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Annex 2. Priority outcomes used in decision-making

Critical outcomes

- Maternal death
- PPH ≥ 1000 mL
- Blood transfusion

Important outcomes

- Severe maternal morbidity: intensive care unit admission
- Severe maternal morbidity: shock
- Postpartum haemorrhage ≥ 500 mL
- Use of additional uterotonics
- Blood loss (mL)
- Postpartum anaemia
- Breastfeeding
- Side-effects[1]
- Maternal well-being
- Maternal satisfaction

[1] This includes any side-effect of the intervention or side-effect requiring treatment, including: nausea, vomiting, headache, abdominal pain, hypotension, shivering, fever and diarrhoea.

Annex 3. Summary and management of declared interests from GDG members

Name	Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Oluwarotimi I Akinola	Content expert and end-user	None declared	Not applicable
Melania Amorim	Content expert and end-user	None declared	Not applicable
Brendan Carvalho	Content expert and end-user	Serves as technical consultant for Gauss Surgical (company that measures peripartum and operative blood loss). Receives share options from Gauss Surgical.	The conflict was not considered serious enough to affect Guideline Development Group (GDG) membership or participation.
Catherine Deneux-Tharaux	Content expert and end-user	None declared	Not applicable
Tippawan Liabsuetrakul	Content expert and end-user	None declared	Not applicable
Martin Meremikwu	Content expert and end-user	None declared	Not applicable
Suellen Miller	Content expert and end-user	Serves as a technical advisor to the Blue Fuzion Group who manufactures and distributes one brand of non-pneumatic anti-shock garment, the LifeWrap. UCSF receives a royalty for the trademark.	The conflict was not considered serious enough to affect GDG membership or participation.
Ashraf Nabhan	Content expert and implementer	None declared	Not applicable
Mari Nagai	Content expert and end-user	None declared	Not applicable
Hayfaa Wahabi	Content expert and end-user	None declared	Not applicable
Dilys Walker	Content expert and end-user	Co-founder and President of the nongovernmental organization PRONTO International. PRONTO designs and implements simulation and team training for obstetric and neonatal emergencies, including postpartum haemorrhage. Professor Walker has donated funds to the organization. PRONTO International has the rights to the low-tech birth simulator, PARTO Pants and the PRONTO Pack simulation training kit.	The conflict was not considered serious enough to affect GDG membership or participation.

Name	Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Andrew Weeks	Content expert and end-user	Chief investigator of the COPE trial, and co-inventor of the Butterfly device to treat postpartum haemorrhage as well as chief investigator of the development study. Both funded by NIHR (United Kingdom) research grants to the University of Liverpool. The University is the device patent holder but, as co-inventor, Professor Weeks would receive a share of the profits.	The conflict was not considered serious enough to affect GDG membership or participation.

Annex 4. Evidence to Decision framework

Question

Following is the question of interest in PICO (population (P), intervention (I), comparator (C), outcome (O)) format:

- For women in the third stage of labour (P), does administration of IV oxytocin for postpartum haemorrhage (PPH) prevention (I) compared with IM oxytocin (C) improve maternal and infant outcomes (O)?

Problem: Preventing the onset of PPH

Perspective: Clinical practice recommendation – population perspective

Population (P): Women in the third stage of labour with vaginal birth

Intervention (I): IV oxytocin

Comparator (C): IM oxytocin

Setting: Hospital or community setting

Subgroups: By type of IV administration; by type of further management.

Priority outcomes (O):[1]

Critical outcomes

- Maternal death
- PPH ≥ 1000 mL
- Blood transfusion

Important outcomes

- Severe maternal morbidity: intensive care unit (ICU) admission
- Severe maternal morbidity: shock
- PPH ≥ 500 mL
- Use of additional uterotonics
- Blood loss (mL)
- Postpartum anaemia
- Breastfeeding
- Side-effects[2]
- Maternal well-being
- Maternal satisfaction

[1] These outcomes reflect the prioritized outcomes used in the development of this recommendation, in *WHO recommendations for the prevention and treatment of postpartum haemorrhage* (2012). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

[2] This includes any side-effect of the intervention or side-effect requiring treatment, including nausea, vomiting, headache, abdominal pain, hypotension, shivering, fever and diarrhoea.

Assessment

Effects of interventions

What is the effect of IV oxytocin versus IM oxytocin for PPH prevention on the priority outcomes?

Research evidence

Summary of evidence

Source and characteristics of studies

Evidence on the effects of IV versus IM oxytocin for the prevention of PPH following vaginal birth was derived from an update of a Cochrane systematic review, which included seven randomized trials (7840 women) *(4)*. Data were extracted from all seven trials (data for 7777 women were analysed; 40 women from one trial were not included because they gave birth by caesarean section after recruitment, and 23 from another trial were excluded because they were given an oxytocin IV infusion after the third stage of labour). Trials were conducted in hospital settings in Argentina, Egypt, Ireland, Mexico, Thailand and Turkey (two trials), between 2010 and 2019. All trials were single-centre except for Egypt (two hospitals).

The number of women included in the trials ranged from 66 to 4913; the largest trial contributed 63% of the total sample. All trials included women with singleton pregnancies only; four trials included women at term and the other three included women at all gestational ages (although most women were at term). All trials recruited women in labour: two trials randomized either when women were in active labour or when delivery was imminent; three randomized when women were admitted to an assessment unit or labour ward while in labour; and two were not specific as to when randomization occurred, though the available information suggests it was when the women were in active labour.

Two trials (1555 women) administered a placebo to all women, while four trials did not mask women or clinicians to the treatment allocation and, in the remaining trial, this was not clear. The third stage of labour was managed actively in four of the included studies (all of these trials used controlled cord traction; two trials delayed cord clamping; and two trials also mention the use of uterine massage). In two studies, active management was not implemented and, in the final study, this was again unclear.

Of the seven trials, four were two-arm trials, two were three-arm trials and one was a four-arm trial. The three-arm trials both compared IM oxytocin with an IV bolus and an IV infusion. In one of these trials, the IV arms were combined into a single pair-wise comparison. In the other three-arm trial, only two arms were eligible for inclusion because one did not take place in the third stage of labour. The four-arm trial compared IM and IV bolus at the birth of the anterior shoulder and at clamping of the cord. The review combined the IM groups and IV groups at each time point to make a single pair-wise comparison.

All seven trials used 10 IU of IM oxytocin, either with the birth of the anterior shoulder or immediately following the birth. All trials used 10 IU of IV oxytocin, given within the same time frame as IM oxytocin. The rates of administration of IV oxytocin differed across trials: over 1 minute (three trials); in 1000 mL saline at a rate of 1 mL/min (one trial); in 500 mL saline solution at a rate of 12 mL/min (one trial); in 10 mL of saline solution slowly administered over 2 minutes (one trial). The largest trial had three arms – the Cochrane review pooled the two IV arms for meta-analysis, combining women receiving IV oxytocin 10 IU in 500 mL saline through a gravity-driven infusion with the roller clamp fully open, with women receiving IV oxytocin 10 IU over 1 minute.

Effects of IV oxytocin compared with IM oxytocin

Maternal death: It is unclear whether the route of administration of oxytocin has an impact on the risk of this outcome as there were no maternal deaths in either group (very low certainty).

PPH ≥1000 mL: Moderate-certainty evidence suggests that the risk of this outcome is probably decreased with IV oxytocin when compared with IM oxytocin (four trials, 6681 women; 47/3692 versus 69/2989; average risk ratio [RR] 0.65, 95% confidence interval [CI] 0.39 to 1.08). However, the 95% CI crosses the line of no effect.

Blood transfusion: High-certainty evidence suggests that women are less likely to need a blood transfusion if they receive IV oxytocin when compared with IM oxytocin (four trials, 6684 women; 19/3693 versus 40/2991; average RR 0.44, 95% CI 0.26 to 0.77).

Severe maternal morbidity – ICU admission: The Cochrane review reported a combined outcome of **serious maternal morbidity**; however, 94% of the pooled effect estimate came from one trial reporting high-dependency unit admissions. Moderate-certainty evidence suggests that IV oxytocin probably decreases the risk of this outcome when compared with IM oxytocin (four trials, 7028 women; 9/3 865 versus 20/3163; average RR 0.47, 95% CI 0.22 to 1.00). However, the 95% CI touches the line of no effect.

PPH ≥ 500 mL: High-certainty evidence suggests that the risk of blood loss ≥ 500 mL decreases when women receive IV oxytocin compared with IM oxytocin (six trials, 7731 women; 201/4 217 versus 253/3514; average RR 0.78, 95% CI 0.66 to 0.92).

Use of additional uterotonics: Low-certainty evidence suggests that the need for additional uterotonics may decrease with IV oxytocin when compared with IM oxytocin (six trials, 7327 women; 179/4014 versus 207/3313; average RR 0.78, 95% CI 0.49 to 1.25). However, the 95% CI crosses the line of no effect.

Blood loss: Six trials (7541 women) in the Cochrane review reported on mean blood loss. The review authors did not pool the data to perform a meta-analysis because the standard deviations (SDs) in the six studies varied considerably. The individual studies suggest that mean blood loss may decrease with IV oxytocin compared with IM oxytocin. However, the review authors observed that the mean blood loss was low across studies, and the difference between the groups is unlikely to be clinically important. The studies contributing data to this outcome varied in their risk of bias, and only two of six trials were at low risk of bias.

Postpartum anaemia: High-certainty evidence suggests that there is little or no difference in the incidence of postpartum anaemia in women who have received IV or IM oxytocin (three trials, 6178 women; 227/3444 versus 222/2744; average RR 0.99, 95% CI 0.84 to 1.16).

Breastfeeding: High-certainty evidence suggests that the route of administration of oxytocin in the third stage of labour makes little or no difference to whether women are **not breastfeeding at hospital discharge** (one trial, 1035 women; 228/517 versus 238/518; average RR 0.96, 95% CI 0.84 to 1.10).

Side-effects: Moderate-certainty evidence suggests that IV oxytocin probably decreases the risk of **any adverse effect reported** when compared with IM administration (one trial, 1035 women; 21/517 versus 27/518; average RR 0.78, 95% CI 0.45 to 1.36). However, the 95% CI crosses the line of no effect.

In terms of specific side-effects, moderate-certainty evidence suggests that the route of oxytocin administration probably makes little or no difference to **hypotension** (four trials, 6468 women; 389/3585 versus 321/2883; average RR 1.01, 95% CI 0.88 to 1.15) and **tachycardia** (two trials, 1513 women; 75/756 versus 85/757; average RR 0.89,

95% CI 0.68 to 1.16). Low-certainty evidence suggests that the route may make little or no difference to **nausea** (two trials, 1515 women; 1/756 versus 1/759; average RR 1.00, 95% CI 0.06 to 15.98), while IV oxytocin may make little or no difference to the risk of **headache** (two trials, 1515 women; 3/756 versus 4/759; average RR 0.75, 95% CI 0.17 to 3.34) and **shivering** (two trials, 1515 women; 2/756 versus 5/759; average RR 0.40, 95% CI 0.08 to 2.06). It is unclear what effect the route of oxytocin administration has on **diarrhoea** (one trial, 480 women; low certainty), **fever** (> 38 °C reported) (one trial, 480 women; low certainty) and **vomiting** (two trials, 1515 women; low certainty) because there were no events in the trials reporting on these outcomes, while sample sizes were relatively small.

Maternal satisfaction: No included trials reported this outcome.

The priority outcomes **shock**, **abdominal pain**, **hypertension** and **maternal well-being** were not reported in the Cochrane review.

Subgroup analyses by type of IV administration

The review analysed the results for two outcomes (PPH ≥ 1000 mL and serious maternal morbidity) by type of IV administration (bolus or infusion). There was no evidence of a difference between the subgroups for severe blood loss. The subgroup effects were unclear for serious maternal morbidity because there were no events in the trials administering oxytocin by IV infusion.

Subgroup analyses by type of management

The review also analysed results for PPH ≥ 1000 mL and serious maternal morbidity by type of further management (with or without active management of the third stage of labour). However, the subgroups were too imbalanced in size to support a meaningful comparison of subgroups by type of further management.

Additional considerations

The Cochrane review authors conducted a sensitivity analysis restricted to trials at low risk of selection bias, for the outcomes PPH ≥ 1000 mL and serious maternal morbidity. Results from trials at low risk of bias suggest that administration of IV oxytocin decreases the risk of PPH ≥ 1000 mL compared with IM oxytocin (two trials, 1512 women; 38/755 versus 60/757; average RR 0.64, 95% CI 0.43 to 0.94).

However, while the point estimate for serious maternal morbidity suggests a probable decrease in risk with IV oxytocin, the 95% CI crosses the line of no effect (two trials, 1515 women; 9/756 versus 19/759; RR 0.47, 95% CI 0.22 to 1.04).

Desirable effects

How substantial are the desirable anticipated effects of IV oxytocin versus IM oxytocin?

Judgement

—	—	—	—	✓	—
Don't know	Varies	Trivial	Small	Moderate	Large

Undesirable effects

How substantial are the undesirable anticipated effects of IV oxytocin versus IM oxytocin?

Judgement

— Don't know	— Varies	— Large	— Moderate	— Small	✓ Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of IV oxytocin versus IM oxytocin?

— No included studies	— Very low	— Low	✓ Moderate	— High

Additional considerations

None.

Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with the route of oxytocin for PPH prevention?

Research evidence

In a review of qualitative studies evaluating "what women want" from intrapartum care, findings indicate that most women want a normal birth (with good outcomes for mother and baby), but acknowledge that medical intervention may sometimes be necessary *(high confidence) (5)*. Most women, especially those giving birth for the first time, are apprehensive about labour and birth *(high confidence)* and wary of medical interventions although, in certain contexts and/or situations, women welcome interventions to address recognized complications *(low confidence)*. Where interventions are introduced, women would like to receive relevant information from technically competent health-care providers who are sensitive to their needs *(high confidence)*.

Findings from another qualitative systematic review exploring perceptions of PPH prevention and treatment among women and providers suggest that women do not recognize the clinical definitions of blood loss or what might be considered "normal" blood loss *(moderate confidence) (6)*. Furthermore, in some low- and middle-income countries (LMICs), women place a greater value on the expulsion of so-called "dirty blood", which they perceive as a normal cleansing process and something that should not be prevented *(moderate confidence)*.

The same review highlighted women's need for information about PPH, ideally given during antenatal care *(moderate confidence)*, and the importance of kind, clinically competent staff with a willingness to engage in shared decision-making around PPH management *(moderate/low confidence)*. In addition, it was found that women are concerned about feelings of exhaustion and anxiety (at being separated from their babies) following PPH, as well as the long-term psychological effects of experiencing PPH and the negative impact this may have on their ability to breastfeed *(moderate/low confidence)*.

Additional considerations

None.

Judgement

— Important uncertainty or variability	— Possibly important uncertainty or variability	✓ Probably no important uncertainty or variability	— No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour IV oxytocin or IM oxytocin?

Judgement

— Don't know	— Varies	— Favours IM oxytocin	— Probably favours IM oxytocin	— Does not favour either	— Probably favours IV oxytocin	✓ Favours IV oxytocin

Resources

How large are the resource requirements (costs) of IV oxytocin for PPH prevention?

Research evidence

A systematic review of the literature updated until 2020 found no direct evidence on the costs and cost-effectiveness of IM oxytocin compared with IV oxytocin to prevent PPH *(7)*.

Additional considerations

Both IV and IM oxytocin require administration by skilled health personnel. However, the administration of IV oxytocin requires intravenous access, which may slightly increase cost due to the need for IV equipment (such as cannulae and IV fluids).

Considering the differences between IV and IM oxytocin in their effectiveness on priority outcomes that are associated with management costs (such as blood transfusion, ICU admission and adverse effects), it is possible that IV oxytocin would be more cost-effective. However, the Guideline Development Group (GDG) noted that the cost-effectiveness would likely differ between higher- and lower-resource settings.

Both IV and IM oxytocin require refrigerated storage and transport, which are not readily available in many low-resource settings *(8)*. Concerns about the quality of oxytocin supplies and wastage due to heat compromise and expiry have been reported *(9)*.

Main resource requirements

Resource	Description
Staff	Oxytocin requires parenteral administration (IV or IM) by skilled health-care personnel.
Training	Training to administer injections, and to monitor and manage expected and unexpected side-effects, is part of standard maternity staff training. However, some additional training may be required if a route of administration of oxytocin is introduced in settings where it has not previously been available.
Supplies	Oxytocin indicative cost: Cost per 10 IU: US$ 0.22–1.19 *(10,11)* IM administration: Needle and syringe IV administration: ■ IV-giving/infusion set, with needle ■ Sterile, disposable IV cannula ■ IV fluids.
Equipment and infrastructure	Cold chain storage and transport costs: Cost per birth is possibly US$ 0.84 in a low-resource setting *(12)*.
Time	IM administration takes 2 minutes. IV administration takes longer, if an IV cannula needs to be put in place for this purpose *(13)*.
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

— Don't know	— Varies	— Large costs	✓ Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

✓ No included studies	— Very low	— Low	— Moderate	— High

Cost-effectiveness

Judgement

✓ Don't know	— Varies	— Favours IM oxytocin	— Probably favours IM oxytocin	— Does not favour either	— Probably favours IV oxytocin	— Favours IV oxytocin

Equity

What would be the impact of IV oxytocin for PPH prevention on health equity?

Research evidence

No direct evidence identified.

Additional considerations

Oxytocin, in injectable form (whether IV or IM), is relatively inexpensive and is already widely available in a range of resource settings *(low to high)*. However, according to the findings from a qualitative systematic review looking at the prevention and treatment of PPH, inconsistent stock levels and the heat sensitivity of the medication may limit its use in low-resource settings in LMICs, particularly in isolated rural areas where the need is arguably greatest *(moderate confidence) (6)*. In some contexts (for example, India and Sierra Leone), supply issues have resulted in women and health-care professionals turning to private suppliers to purchase oxytocin, at additional cost to themselves, in order to fulfil guideline recommendations. These challenges are likely to affect both IV oxytocin and IM oxytocin.

The 2015 World Health Organization (WHO) State of inequality report indicates that women who are poor, least educated and who reside in rural areas have lower coverage of health interventions and worse health outcomes than more advantaged women *(14)*. IV oxytocin may decrease equity, as it can be more difficult for women to access it (due to the need for IV access).

Judgement

— Don't know	— Varies	— Reduced	✓ Probably reduced	— Probably no impact	— Probably increased	— Increased

Acceptability

Is IV oxytocin for PPH prevention acceptable to key stakeholders?

Research evidence

No direct evidence relating to the acceptability of (or preference for) a particular administration route for oxytocin from either women or health-care providers was identified.

Additional considerations

IV oxytocin is widely used internationally and in a range of resource settings *(low to high)*.

Indirect findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment by women and health-care providers indicate that providers recognize the benefits of using oxytocin (usually via a single IV injection) to prevent PPH and hasten the delivery of the placenta *(moderate confidence) (6)*. However, in some LMIC settings, providers hold the perception that the medication may cause retained placenta when administered preventatively or may even contribute to PPH when given to induce labour *(moderate confidence)*. In rural LMIC settings where access to health facilities may be limited, community-based health providers (usually traditional birth attendants) prefer to use herbal medicines with uterotonic properties *(moderate confidence)*, while in several high-income countries, experienced midwives use expectant management and make selective use of guideline recommendations

(ignoring oxytocin use), especially if the birth is perceived to be normal *(moderate confidence)*. There were no findings from studies of women's perceptions relating to the acceptability of oxytocin.

The GDG noted the lack of direct evidence on acceptability. However, they noted the aforementioned evidence that women prefer a normal birth and considered that, in some situations, the presence of an IV line and/or the administration of IV fluids around the time of childbirth may cause some discomfort or restrict a woman's mobility. However, in situations where a woman already has IV access in place (for other medical reasons), it is likely that women would find IV oxytocin administration to be acceptable.

Judgement

✓ Don't know	— Varies	— No	— Probably No	— Probably Yes	— Yes

Feasibility

Is IV oxytocin for PPH prevention feasible to implement?

Research evidence

No direct evidence relating to the feasibility of a particular administration route for oxytocin from either women or health-care providers was identified. However, IV oxytocin is widely used internationally and in a range of resource settings (low to high).

Additional considerations

Indirect findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment among women and health-care providers suggest that resource constraints may influence effective use of oxytocin for PPH prevention, particularly in LMICs *(high confidence) (6)* . Inconsistent supplies and concerns about oxytocin storage in areas with limited/inconsistent electricity hinder utilization, and a lack of experienced staff to administer the injection limits its use in certain contexts *(high confidence)*. In a wide variety of settings, health-care providers feel they need more training in PPH management, as well as specific training on when/how to administer oxytocin *(high confidence)*. In some LMIC settings, task shifting had been introduced to address staff shortages or increase coverage, and the success of this strategy was largely dependent on the ability of health-care professionals to build trustworthy relationships with traditional birth attendants or community health workers *(moderate confidence) (6)*. There were no findings from the reviewed studies on women's perceptions relating to the feasibility of this particular intervention.

Injectable oxytocin is already widely available in a range of resource settings (low to high) and has multiple applications (such as PPH prevention and treatment as well as labour induction). Oxytocin (10 IU in 1 mL for injection) is listed in the *WHO model list of essential medicines (3)*.

The GDG noted, however, that lack of access to equipment and fluids for IV administration, as well as the need to have staff that can safely manage IV infusions, may limit feasibility of IV oxytocin, particularly in lower-level facilities in limited-resource settings.

Judgement

— Don't know	✓ Varies	— No	— Probably No	— Probably Yes	— Yes

Summary of judgements table

Desirable effects	— Don't know	— Varies		— Trivial	— Small	✓ Moderate	— Large
Undesirable effects	— Don't know	— Varies		— Large	— Moderate	— Small	✓ Trivial
Certainty of the evidence	— No included studies			— Very low	— Low	✓ Moderate	— High
Values				— Important uncertainty or variability	— Possibly important uncertainty or variability	✓ Probably no important uncertainty or variability	— No important uncertainty or variability
Balance of effects	— Don't know	— Varies	— Favours IM oxytocin	— Probably favours IM oxytocin	— Does not favour either	— Probably favours IV oxytocin	✓ Favours IV oxytocin
Resources required	— Don't know	— Varies	— Large costs	✓ Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings
Certainty of the evidence on required resources	✓ No included studies			— Very low	— Low	— Moderate	— High
Cost-effectiveness	✓ Don't know	— Varies	— Favours IM oxytocin	— Probably favours IM oxytocin	— Does not favour either	— Probably favours IV oxytocin	— Favours IV oxytocin
Equity	— Don't know	— Varies	— Reduced	✓ Probably reduced	— Probably no impact	— Probably increased	— Increased
Acceptability	✓ Don't know	— Varies		— No	— Probably No	— Probably Yes	— Yes
Feasibility	— Don't know	✓ Varies		— No	— Probably No	— Probably Yes	— Yes

Summary of findings table

Question: IV compared with IM oxytocin for the third stage of labour
Setting: Hospitals (Argentina, Egypt, Ireland, Mexico, Thailand and Turkey)
Reference: Oladapo OT, Okusanya BO, Abalos E, Gallos ID, Papadopoulou A. Intramuscular versus intravenous prophylactic oxytocin for the third stage of labour. Cochrane Database Syst Rev (in press).

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consid-erations	IV oxytocin	IM oxytocin	Relative (95% CI)	Absolute (95% CI)		
MATERNAL DEATH												
4	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	0/3865 (0.0%)	0/3163 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
SEVERE PPH ≥ 1000 ML												
4	randomized trials	not serious	not serious	not serious	serious[c]	none	47/3692 (1.3%)	69/2989 (2.3%)	**Average RR 0.65** (0.39 to 1.08)	**8 fewer per 1000** (from 14 fewer to 2 more)	⨁⨁⨁◯ MODERATE	CRITICAL
BLOOD TRANSFUSION												
4	randomized trials	not serious	not serious	not serious	not serious	none	19/3693 (0.5%)	40/2991 (1.3%)	**Average RR 0.44** (0.26 to 0.77)	**7 fewer per 1000** (from 10 fewer to 3 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
SERIOUS MATERNAL MORBIDITY (ORGAN FAILURE, COMA, ICU ADMISSION, HYSTERECTOMY OR AS DEFINED BY THE STUDY AUTHORS)												
4	randomized trials	not serious	not serious	not serious	serious[d]	none	9/3865 (0.2%)	20/3163 (0.6%)	**Average RR 0.47** (0.22 to 1.00)	**3 fewer per 1000** (from 5 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
BLOOD LOSS ≥ 500 ML												
6	randomized trials	not serious	not serious	not serious	not serious	none	201/4217 (4.8%)	253/3514 (7.2%)	**Average RR 0.78** (0.66 to 0.92)	**16 fewer per 1000** (from 24 fewer to 6 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consid-erations	IV oxytocin	IM oxytocin	Relative (95% CI)	Absolute (95% CI)		
USE OF ADDITIONAL UTEROTONICS												
6	randomized trials	not serious	serious[e]	not serious	serious[c]	none	179/4014 (4.5%)	207/3313 (6.2%)	**Average RR 0.78** (0.49 to 1.25)	**14 fewer per 1000** (from 32 fewer to 16 more)	⨁⨁◯ LOW	IMPORTANT
POSTPARTUM ANAEMIA												
3	randomized trials	not serious	not serious	not serious	not serious	none	227/3444 (6.6%)	222/2744 (8.1%)	Average RR 0.99 (0.84 to 1.16)	**1 fewer per 1000** (from 13 fewer to 13 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
NOT BREASTFEEDING AT HOSPITAL DISCHARGE												
1	randomized trials	not serious	not serious	not serious	not serious	none	228/517 (44.1%)	238/518 (45.9%)	**Average RR 0.96** (0.84 to 1.10)	**18 fewer per 1000** (from 74 fewer to 46 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
ANY ADVERSE EFFECT REPORTED												
1	randomized trials	not serious	not serious	not serious	serious[f]	none	21/517 (4.1%)	27/518 (5.2%)	**Average RR 0.78** (0.45 to 1.36)	**11 fewer per 1000** (from 29 fewer to 19 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
ABDOMINAL PAIN – NOT REPORTED												
—	—	—	—	—	—	—	—	—	—	—	—	IMPORTANT
DIARRHOEA												
1	randomized trials	not serious	not serious	not serious	very serious[b]	none	0/239 (0.0%)	0/241 (0.0%)	not estimable		⨁⨁◯ LOW	IMPORTANT
FEVER > 38 °C												
1	randomized trials	not serious	not serious	not serious	very serious[b]	none	0/239 (0.0%)	0/241 (0.0%)	not estimable		⨁⨁◯ LOW	IMPORTANT

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consid-erations	IV oxytocin	IM oxytocin	Relative (95% CI)	Absolute (95% CI)		
HEADACHE												
2	randomized trials	not serious	not serious	not serious	very serious[f,g]	none	3/756 (0.4%)	4/759 (0.5%)	**Average RR 0.75** (0.17 to 3.34)	**1 fewer per 1000** (from 4 fewer to 12 more)	⨁⨁⨀ LOW	IMPORTANT
HYPERTENSION - NOT REPORTED												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
HYPOTENSION												
4	randomized trials	serious[a]	not serious	not serious	not serious	none	389/3585 (10.9%)	321/2883 (11.1%)	**Average RR 1.01** (0.88 to 1.15)	**1 more per 1000** (from 13 fewer to 17 more)	⨁⨁⨁⨀ MODERATE	IMPORTANT
NAUSEA												
2	randomized trials	not serious	not serious	not serious	very serious[f,g]	none	1/756 (0.1%)	1/759 (0.1%)	**Average RR 1.00** (0.06 to 15.98)	**0 fewer per 1000** (from 1 fewer to 20 more)	⨁⨁⨀ LOW	IMPORTANT
SHIVERING												
2	randomized trials	not serious	not serious	not serious	very serious[f,g]	none	2/756 (0.3%)	5/759 (0.7%)	**Average RR 0.40** (0.08 to 2.06)	**4 fewer per 1000** (from 6 fewer to 7 more)	⨁⨁⨀ LOW	IMPORTANT
TACHYCARDIA												
2	randomized trials	not serious	not serious	not serious	serious[c]	none	75/756 (9.9%)	85/757 (11.2%)	**Average RR 0.89** (0.68 to 1.16)	**12 fewer per 1000** (from 36 fewer to 18 more)	⨁⨁⨁⨀ MODERATE	IMPORTANT
VOMITING												
2	randomized trials	not serious	not serious	not serious	very serious[b]	none	0/756 (0.0%)	0/759 (0.0%)	not estimable		⨁⨁⨀ LOW	IMPORTANT

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consid-erations	IV oxytocin	IM oxytocin	Relative (95% CI)	Absolute (95% CI)		
MATERNAL WELL-BEING – NOT REPORTED												
—	—	—	—	—	—	—	—	—	—	—	—	IMPORTANT
MATERNAL SATISFACTION – NOT REPORTED												
—	—	—	—	—	—	—	—	—	—	—	—	IMPORTANT

CI: confidence interval; **ICU**: intensive care unit; **IM**: intramuscular; **IV**: intravenous; **RR**: risk ratio

[a] Majority of pooled effect provided by study (or studies) at moderate risk of bias.
[b] No events, not estimable.
[c] Wide CI including both line of no effect, and appreciable decrease in risk with IV oxytocin.
[d] Wide CI touching line of no effect, and also including appreciable decrease in risk with IV oxytocin.
[e] Severe statistical heterogeneity (I^2=61%).
[f] Wide CI including both appreciable decrease and appreciable increase in risk with IV oxytocin.
[g] Few events.

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